Xenotransplantation: progress and promise

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Extensive research in xenotransplantation is being propelled by the critical shortage of allotransplants. About a third of the patients on organ waiting lists in the United States die for lack of available organs, and in the United Kingdom fewer than 30% of those waiting for kidneys receive them each year.[1–3] The human toll of suffering in patients who need transplants is great, and their quality of life is poor.

Summary points

Xenotransplantation research is driven by the acute shortage of available allotransplants

Although one longstanding problem, hyperacute rejection of xenotransplants, is being overcome, daunting immunological barriers remain

Great attention must be given to the physiological functions of porcine organs in human beings

Worries over the infectious disease potential of porcine xenotransplants are easing

Ethical concerns over xenotransplants, including the challenge of identifying patients who might be approached as subjects of reinitiated clinical trials, are being explored

This update focuses on whole organ xenotransplants. It draws on the latest published studies and the assessments at two recent meetings—a conference of US and UK scientists, ethicists, and policy experts in New York in May 1999, and the June 1999 meeting of the xenotransplantation subcommittee of the US Food and Drug Administration's Center for Biologics Evaluation and Research.

Research is currently being conducted in all the critical areas of xenotransplantation, and this will, it is hoped, make xenotransplants safe and effective for human beings. These critical areas include immunological barriers, physiological functioning, infectious disease risks, and pivotal ethical issues.

Immunological barriers

Over time, xenotransplantation has proved to be daunting because of organ rejection. Rejection occurs in several stages: hyperacute rejection, acute vascular rejection, cellular rejection, and chronic rejection.[2–4] Hyperacute rejection and acute vascular rejection are mediated by antibodies against oligosaccharide determinants on pig vascular endothelium.[5] These forms of rejection occur rarely with human allografts, which are associated more with cellular and chronic rejection.

Hyperacute rejection

Hyperacute rejection is now being overcome. While several approaches are possible, the most successful currently involves producing transgenic pigs that express human complement regulatory proteins capable of inhibiting the injurious effect of antibody mediated complement activation on the vascularised pig organ.[6 7] One biotechnology company, for example, has transplanted transgenic pig organs into non-human primates and has achieved a hyperacute rejection rate of less than 2%.

Acute vascular rejection

Part of the problem in overcoming acute vascular rejection is the fact that the biology of this form of rejection is incompletely understood. Reports from two biotechnology firms presented at the June meeting of the xenotranplantation committee of the Food and Drugs Administration Center for Biologics Evaluation and Research indicated that the organ survival times of transgenic pig hearts and kidneys in non-human primates (hereafter referred to as primates) varied from a few days to several weeks. Effective immunosuppressive regimens for primates are in development, and some of the regimens now used could not be tolerated by humans. Researchers cannot yet control acute vascular rejection. However, progress is being made on several fronts, including the development of new immunosuppressive drugs and further attempts to genetically engineer pigs.

Cellular rejection

Although the strength of cellular rejection in xenografts remains uncertain, it is expected to be stronger than that seen in allografts. It is also anticipated that chronic rejection (for example, graft arteriosclerosis) of xenotransplants will be more aggressive than in allografts. Overcoming these barriers will probably require severe and sustained concentrations of immunosuppressive drugs or breakthroughs in the development of human immunological tolerance to porcine organs.[8]

Physiological functioning

Extensive research will be needed to determine whether animal organs can replace the physiological functions of human organs—research is being carried out in fields such as anatomical design, metabolism, hormonal function, and blood viscosity and coagulation.[9] One biotechnology company reported to the Food and Drug Administration meeting that pig to primate kidney transplants function well on several levels, but lack compatibility in respect of erythropoietin function.

Researchers now predict that pig to human transplants of hearts, kidneys, and lungs will be physiologically feasible. However, this is not the case for whole organ liver transplants, where differences between many of the proteins manufactured in the liver may prohibit adequate function. Lung transplants will also require far more research into physiology and risks of infectious disease.

Risks of infectious disease

The infectious disease risks of xenotransplants pose a problem for the recipients of organ transplants and the public at large. The public health risk that xenotransplantation might

create a new infectious disease epidemic represents a major ethical concern that is the subject of widespread discussion and controversy.[10 11]

Two years ago the risk that pig to human transplants might spread infectious disease were regarded as so worrisome that the Food and Drug Administration placed a hold on ongoing clinical trials involving new drug developments and cellular xenotransplants—porcine islet cells, hepatocytes, and so on. The hold was to continue until the companies sponsoring these trials developed assays that could detect and identify potential porcine endogenous retroviruses that had just been shown to infect human cells in vitro.[12–14] Because endogenous retroviruses are found in the DNA of all mammalian species, they cannot be "bred out" of xenotransplants. In contrast, the many other infectious diseases of pigs can be excluded by breeding and safety measures that produce pathogen free colonies.[15]

Several developments since October 1997 support the conclusion that there is no appreciable current evidence of porcine endogenous retrovirus infection in human recipients of xenotransplants.[16 17] Although most of the human recipients were exposed to porcine tissue for relatively brief periods of time, evidence from independent researchers and several sponsors of trials now indicates that porcine endogenous retrovirus infectivity is either non-existent or confined to very low levels that probably result from the presence of retrovirus in source cells. These reassuring findings led the Food and Drug Administration to conclude that six of the 10 sponsors of clinical trials involving xenotransplant cells had addressed adequately the safety concerns identified in 1997.

With regard to public health risks, evidence on porcine endogenous retrovirus infectivity in human cells in vitro[11 12] and the creation and onset of the HIV virus[18] led the Food and Drug Administration to decide in April 1999 that protocols involving primate xenografts in humans should not be submitted until their risks are known, addressed, and discussed publicly.[19] This accords with a conclusion in the report from the UK Advisory Group on the Ethics of Xenotransplantation that primates should not be used as source animals for humans.[20]

The infectious disease risks posed by porcine endogenous retrovirus is a topic of continued concern and discussion. Even though the Food and Drug Administration knew that sensitive tests for porcine endogenous retrovirus have recently been developed, its xenotransplant subcommittee called last June for greater standardisation and quality control of infectious diseases assays, new assays to test viral expression in plasma, and other yardstick safety measures that should be developed and refined.

Ethical issues

Although the infectious disease risks of xenotransplants is a major ethical concern, all of the topics discussed above pertain to ethics because they are pivotal to an analysis of the risks and benefits of clinical trials. These scientific ethical issues pertain to the first required level of ethical analysis of clinical research,

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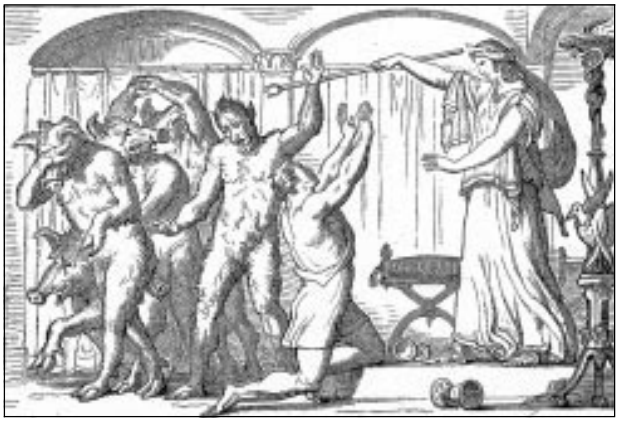
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which is discussed under the rubric of "beneficence" in the 1979 "Belmont report" of the US National Commission,[21] and is addressed in the regulations of respective nations and in official reports on the ethics of xenotransplantation from the United States and the United Kingdom.[1 20]

Additional ethical issues include the use of animals, genetic alterations of animal species, the complexities of informed consent for research subjects, the justice of including or excluding respective groups of human subjects in clinical trials, and the imperative of educating the public lest it feel that researchers and biotechnology firms are forging ahead without public awareness.[1 11 20 22 23]

A critical and neglected ethical issue involves identifying the populations of patients who might become the early subjects of reinitiated clinical trials.[22–24] The UK Kennedy report recommends that children and others incapable of giving informed and legally valid consent should be excluded until "initial concerns about safety and efficacy have been satisfactorily resolved."[20] But how will these initial concerns be resolved?

This topic was discussed at length at the June meeting of the xenotransplantation committee of the Food and Drug Administration's Center for Biologics Evaluation and Research. Viewed as initial and far from definitive, the discussion first focused on what kinds of preclinical data are necessary to assure benchmark levels of success and safety in human trials. The subcommittee agreed that, given our greater knowledge of human immunological suppression and infection control, the success of human trials is likely to be greater than the present pig to primate transplants. Yet most members of the subcommittee believed that human trials should not be allowed until preclinical studies show more success. Most recommended that before human trials resume, the success rate of pig to primate transplants should be raised from the present 50% organ survival rate for less than one month to a 90% survival rate for two months, and a 50% rate for three months.

Discussion then turned to populations of patients who might stand to benefit from clinical trials. Xenotransplants as bridges to allotransplants might improve the survival chances and quality of life of some patients. And xenotransplants could serve as definitive transplant treatment for some groups of patients who are excluded from allotransplant waiting lists. Several groups were identified and discussed under the proviso that preclinical data do not yet warrant a renewal of clinical trials. Starting these trials too early could bring more harm than benefit to patients and adversely affect public opinion and current and future progress.

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